# Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study

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## Summary

**Background** Patients with COVID-19 who develop severe acute respiratory distress syndrome (ARDS) can have symptoms that rapidly evolve to profound hypoxaemia and death. The efficacy of extracorporeal membrane oxygenation (ECMO) for patients with severe ARDS in the context of COVID-19 is unclear. We aimed to establish the clinical characteristics and outcomes of patients with respiratory failure and COVID-19 treated with ECMO.

**Methods** This retrospective cohort study was done in the Paris–Sorbonne University Hospital Network, comprising five intensive care units (ICUs) and included patients who received ECMO for COVID-19 associated ARDS. Patient demographics and daily pre-ECMO and on-ECMO data and outcomes were collected. Possible outcomes over time were categorised into four different states (states 1–4): on ECMO, in the ICU and weaned off ECMO, alive and out of ICU, or death. Daily probabilities of occupation in each state and of transitions between these states until day 90 post-ECMO onset were estimated with use of a multi-state Cox model stratified for each possible transition. Follow-up was right-censored on July 10, 2020.

**Findings** From March 8 to May 2, 2020, 492 patients with COVID-19 were treated in our ICUs. Complete day-60 follow-up was available for 83 patients (median age 49 [IQR 41–56] years and 61 [73%] men) who received ECMO. Pre-ECMO, 78 (94%) patients had been prone-positioned; their median driving pressure was 18 (IQR 16–21) cm $H_2O$ and $PaO_2/FiO_2$ was 60 (54–68) mm Hg. At 60 days post-ECMO initiation, the estimated probabilities of occupation in each state were 6% (95% CI 3–14) for state 1, 18% (11–28) for state 2, 45% (35–56) for state 3, and 31% (22–42) for state 4. 35 (42%) patients had major bleeding and four (5%) had a haemorrhagic stroke. 30 patients died.

**Interpretation** The estimated 60-day survival of ECMO-rescued patients with COVID-19 was similar to that of studies published in the past 2 years on ECMO for severe ARDS. If another COVID-19 outbreak occurs, ECMO should be considered for patients developing refractory respiratory failure despite optimised care.

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## Introduction

The 2019 outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly evolved into a worldwide pandemic, with more than 17 million cases of COVID-19 as of July 30, 2020. In France, many disease clusters were identified early in March, 2020, with Paris and its surrounding area (Greater Paris) reporting the most cases. COVID-19 can lead to acute respiratory failure requiring intensive care unit (ICU) admission and mechanical ventilation. However, its most serious forms can rapidly evolve to severe acute respiratory distress syndrome (ARDS) with profound hypoxaemia and death, despite lung-protective mechanical ventilation, including prone-positioning.[1,2]

In 2018, the extracorporeal membrane oxygenation (ECMO) to rescue Lung Injury in severe ARDS (EOLIA; n=249) trial showed that although mortality in the ECMO group was lower at 35% compared with 46% in the control group, the difference was not significant (relative risk 0·76 [95% CI 0·55–1·04]; p=0·09).[3] A post-hoc Bayesian analysis of EOLIA data later showed a high likelihood of an ECMO survival benefit for severe ARDS, as defined by the EOLIA entry criteria.[4] Accordingly, international organisations[5,6] and experts in the field[7,8] recommended ECMO for patients who were critically ill with COVID-19 following the initial outbreak in China, further stating that it should be provided in high-volume specialised centres, and a mobile ECMO team should retrieve patients on ECMO from other centres. However, survival was very low in Chinese case series of ECMO-treated patients with COVID-19,[9,10] raising concerns about the usefulness of ECMO in this setting.[11]

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See Online for appendix

## Research in context

### Evidence before this study
COVID-19 can lead to acute respiratory failure requiring intensive care unit (ICU) admission and mechanical ventilation. However, its most serious forms can rapidly evolve to severe acute respiratory distress syndrome (ARDS) with profound hypoxaemia and death, despite lung-protective mechanical ventilation, including prone-positioning. Extracorporeal membrane oxygenation (ECMO) efficacy in this setting is unknown. We searched PubMed for full papers in any language published in peer-reviewed journals up to July 10, 2020, with the terms "ECMO" and "2019 novel coronavirus", "2019-nCoV", "COVID-19", or "SARS-CoV-2". We identified 21 articles that reported cases of patients infected with SARS-CoV-2 who received ECMO for acute respiratory failure. However, these studies included only a limited number of patients (n=1 to n=32), with limited information on patient characteristics, management, and outcomes. Very few of them reported patient survival beyond day 30 post-ECMO onset, precluding any conclusion regarding the usefulness of ECMO in this setting.

### Added value of this study
This retrospective study, with 83 patients included and a complete follow-up until day 60 post-ECMO initiation is, to our knowledge, the largest to date reporting the outcomes after rescue ECMO for the most severe forms of COVID-19 ARDS, in the Paris–Sorbonne University Hospital Network (Paris, France), the principal hospital referral network for ICU care in Greater Paris, including one of the largest European ECMO centres (Pitié–Salpêtrière Hospital). Our patients' pre-ECMO characteristics indicated extreme ARDS severity (median $PaO_2/FiO_2$, 60 [IQR 54–68] mm Hg) although 94% had been prone-positioned before ECMO onset. The estimated probability of death 60 days post-ECMO initiation was 31% (95% CI 22–42). 35 (42%) had major bleeding and four (5%) patients had a haemorrhagic stroke.

### Implications of all the available evidence
Contrary to preliminary results that indicated dismal outcomes with 84–100% mortality of patients with COVID-19 given ECMO, the estimated 31% probability of day-60 mortality for our patients on ECMO was similar to those ECMO-treated in the EOLIA trial or the large prospective LIFEGARD registry. Should another COVID-19 wave occur, ECMO should be considered early for patients developing profound respiratory failure, despite optimised conventional care, including prone-positioning. Longer-term follow-up of these patients is now needed to evaluate COVID-19's potential pulmonary, physical, and psychological sequelae.

We aimed to establish the characteristics and outcomes of patients who received ECMO for laboratory-confirmed SARS-CoV-2 infection in the Paris–Sorbonne University Hospital Network ICUs, the principal hospital referral network for ICU care in Greater Paris, including one of the largest European ECMO centres (Pitié–Salpêtrière Hospital).

## Methods

### Study design and participants
This retrospective cohort study was done in the Paris–Sorbonne University Hospital Network ICUs (three at La Pitié–Salpêtrière Hospital, one in Saint-Antoine Hospital, and one in Tenon Hospital), which cared for patients with COVID-19 with severe ARDS. All consecutive adult patients with laboratory confirmed SARS-CoV-2 infection, documented by real-time RT-PCR on nasopharyngeal swabs, or lower respiratory tract aspirates,[12] and who received venoarterial-ECMO or venovenous-ECMO for severe ARDS were included. Patients who received ECMO for isolated refractory cardiogenic shock were excluded. ECMO support was provided at Pitié–Salpêtrière and Tenon hospital ICUs, while Saint-Antoine hospital ICU cared for patients either before ECMO cannulation or after ECMO decannulation.

The Sorbonne-University Ethics Committee (CER-SU-2020-46) approved the protocol. In accordance with the ethical standards of French legislation (Committees for the Protection of Human Subjects), informed consent for demographic, physiological, and hospital-outcome data analyses was not obtained because this observational study did not modify existing diagnostic or therapeutic strategies. Only non-opposition of the patient or their legal representative for use of the data was obtained.

### Procedures
In a context of ECMO resource constraints, all ECMO proposals in Greater Paris were centralised at Pitié–Salpêtrière Hospital. Once contacted, indications for ECMO were evaluated in a staff meeting, including at least two intensivists. Patients eligible for ECMO had to fulfill ARDS criteria,[13] and one of the following disease severity criteria, despite ventilator optimisation (fraction of inspired oxygen [$FiO_2$] ≥80%, tidal volume set at 6 mL/kg predicted bodyweight, and positive end-expiratory pressure [PEEP] ≥10 cm of water): (1) partial pressure of arterial oxygen ($PaO_2$) over a $FiO_2$ ratio of less than 50 mm Hg for more than 3 h; (2) $PaO_2/FiO_2$ less than 80 mm Hg for more than 6 h; or (3) arterial blood pH less than 7·25 with a partial pressure of arterial carbon dioxide ($PaCO_2$) of 60 mm Hg or more for 6 h or more.[3]

Physicians were strongly encouraged to use neuromuscular blocking agents and prone-positioning before ECMO. ECMO contraindications were: age older than 70 years, severe comorbidities (eg, advanced cardiac, respiratory, or liver failure; metastatic cancer; or haematological malignancies), cardiac arrest (except when cardiopulmonary resuscitation was provided immediately and the low-flow time was <15 minutes), refractory multiorgan failure or Simplified Acute Physiology Score (SAPS) II more than 90, irreversible neurological injury, and mechanical ventilation for more than 10 days.

Once the indication was approved, the Pitié–Salpêtrière mobile ECMO retrieval team (MERT), comprising a cardiovascular surgeon and a perfusionist, was sent to the patient's bedside for ECMO cannulation, as described previously.[14,15] Our MERT was available 24 h per day, 7 days a week. Once ECMO had been implanted, the patient was transferred by a Service d'Aide Medicale d'Urgence ambulance with the MERT to one of the Paris–Sorbonne University Hospital Network ICUs.

ECMO cannulation was done percutaneously under ultrasonography guidance by a cardiovascular surgeon wearing full personal protective equipment (ie, respirator FFP2 or N95 mask, gown, goggles, and gloves). For venovenous-ECMO, blood drainage with a large cannula (25–29 Fr) inserted into the common femoral vein, and returned through the right internal jugular vein was strongly recommended. For venoarterial-ECMO, a venous drainage cannula (23–29 Fr) was inserted into the common femoral vein, an arterial return cannula (15–19 Fr) into the common femoral artery, and an additional anterograde perfusion cannula was systematically inserted into the superficial femoral artery to prevent leg ischaemia. Pump speed was adjusted to obtain blood-oxygen saturation at more than 90%. Optimal cannula positioning was verified by ultrasonography and chest X-ray. Following early reports of severe COVID-19 associated coagulopathy[16–18] and frequent thromboembolic events on ECMO, including massive pulmonary embolism,[19,20] we decided to increase the targeted activated partial thromboplastin time for anticoagulation of venovenous ECMO with unfractionated heparin to 60–75 s or anti-Xa activity 0·3–0·5 IU/mL (respective values were 40–55 s or 0·2–0·3 IU/mL in the EOLIA trial[3]) before we treated our first patients with COVID-19 ARDS. Plasma-free haemoglobin and plasma fibrinogen concentrations were monitored daily. The haemoglobin threshold for red blood cell transfusion was 7–8 g/dL (or ≤10 g/dL when hypoxaemia persisted); platelet transfusions were discouraged except for severe thrombocytopenia ($<50\times10^9$ cells per L) or thrombocytopenia of more than $100\times10^9$ cells per L with bleeding. To enhance protection against ventilator-induced lung injury, ultra-protective lung ventilation on ECMO was recommended,[3,21] by targeting lower mechanical power delivered to the lungs and lower tidal volume, respiratory rate, and airway and driving pressures. Early prone-positioning on ECMO was encouraged in the absence of haemodynamic instability and contraindications for prone-positioning (ie, massive haemoptysis requiring an immediate surgical or interventional radiology procedure; deep venous thrombosis treated for less than 2 days, or single anterior chest tube with air leaks).[3,21,22] Patients were assessed daily for possible

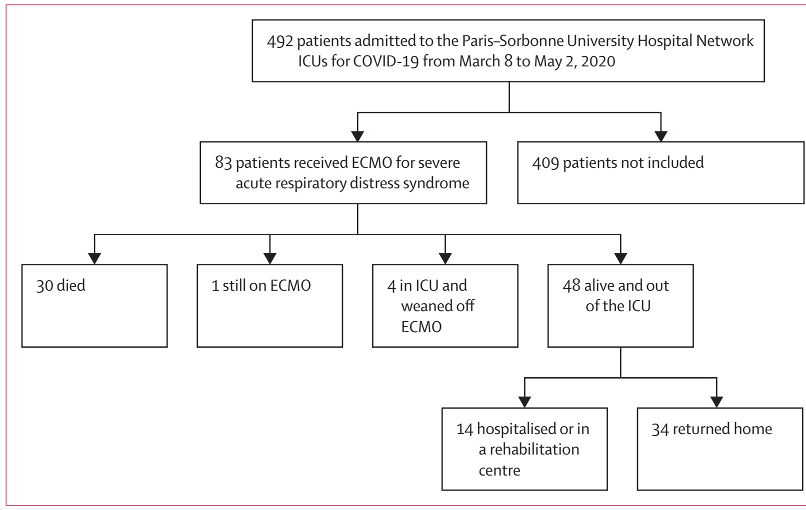


*Figure 1:* **Study profile**
Study profile for patients included in this study, and their outcomes at July 10, 2020. ICU=intensive care unit. ECMO=extracorporeal membrane oxygenation.

ECMO weaning with use of the EOLIA clinical and physiological criteria.[3,21]

Information recorded before ECMO comprised age, sex, body-mass index, comorbidities, SAPS II,[23] Sequential Organ-Failure Assessment score,[24] Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score,[25] date of first symptoms, and hospital and ICU admissions. Information collected before ECMO implantation comprised previous rescue therapies, the date mechanical ventilation started, ventilator settings (mode, PEEP, $FiO_2$, respiratory rate, tidal volume, plateau pressure [$P_{plat}$]), arterial blood-gas parameters, and routine laboratory values. Driving pressure (ΔP) was defined as $P_{plat}$ minus PEEP and mechanical power (J/min) was calculated as follows[26]:

$$\text{mechanical power} = 0\cdot098 \times \text{tidal volume} \times \text{respiratory rate} \times \left(\text{peak pressure} - \frac{1}{2} \times \Delta P\right)$$

Ventilatory ratio was calculated as[27]:

$$\frac{[\text{minute ventilation} \times PaCO_2]}{[\text{predicted bodyweight} \times 100 \times 37\cdot5]}$$

An expanded dataset including mechanical ventilation settings, arterial blood gases, adjuvant therapies on ECMO, and ECMO-related complications was noted daily from day 1–7, then every 7 days until ECMO day 60, ECMO weaning, or death, whichever occurred first. ECMO-related complications and organ dysfunction included major bleeding, blood-cell transfusions, massive haemolysis, ECMO-circuit change, severe thrombocytopenia ($<50\times10^9$ cells per L, occurring during the first

3 days of ECMO), stroke, renal replacement therapy, proven pulmonary embolism, pneumothorax, ventilator-associated pneumonia, bacteraemia, and cardiac arrest. Major bleeding was defined as requiring two or more units of packed red blood cells due to an obvious haemorrhagic event, necessitating a surgical or interventional procedure, an intracerebral haemorrhage, or a bleed causing a fatal outcome, while massive haemolysis was defined as plasma-free haemoglobin of more than 500 mg/L associated with clinical signs of haemolysis.

### Outcomes

Patient outcomes comprised the following endpoints: on ECMO, in the ICU and weaned off ECMO, alive and out of ICU, or died on days 28, 40, 50, 60, 70, 80, and 90 after ECMO implantation. Time spent in each state was calculated for the whole population of 83 patients, with right-censoring of patients who did not reach the final absorbing state at later timepoints (day 70, 80, or 90). Other outcomes comprised ICU and ECMO-related complications.

### Statistical analysis

Patient characteristics are expressed as n (%) for categorical variables, mean (SD) for continuous variables, or median (IQR), as appropriate.

To better describe patients' trajectories in the ICU over time, a multi-state model[28] was used. Briefly, this framework considers that a patient can go through different states during follow-up. Herein, the starting time was the ECMO initiation day, making on ECMO the initial state for all patients, potentially followed by two intermediate

| | All patients (N=83) | Alive and discharged from the ICU (n=48)* | Alive and still in the ICU (n=5)† | Died (n=30) |
|---|---|---|---|---|
| Age, years | 49 (41–56) | 45 (38–53) | 49 (43–58) | 52 (48–58) |
| Sex | | | | |
| Male | 61 (73%) | 34 (71%) | 3 (60%) | 24 (80%) |
| Female | 22 (27%) | 14 (29%) | 2 (40%) | 6 (20%) |
| Body-mass index, kg/cm² | 30·4 (27·9–34·1) | 31·1 (27·7–34·6) | 28·6 (26·3–30·4) | 29·4 (28·2–33·8) |
| Simplified Acute Physiology Score II | 45 (29–56) | 42 (28–52) | 56 (53–68) | 50 (31–64) |
| RESP score | 4 (2–5) | 4 (3–5) | 4 (2–4) | 3 (1–5) |
| Total SOFA score‡ | 12 (9–13) | 11 (8–12) | 9 (8–17) | 12 (10–16) |
| Renal component of the SOFA score of 3 or greater | 14 (17%) | 5 (10%) | 2 (40%) | 7 (23%) |
| Cardiovascular component of the SOFA score of 3 or greater | 42 (51%) | 23 (48%) | 2 (40%) | 17 (57%) |
| Haematological component of the SOFA score of 3 or greater | 2 (2%) | 0 | 0 | 2 (7%) |
| Comorbidities | | | | |
| Hypertension | 32 (39%) | 17 (35%) | 2 (40%) | 13 (43%) |
| Diabetes | 26 (31%) | 13 (27%) | 2 (40%) | 11 (37%) |
| Ischaemic cardiomyopathy | 4 (5%) | 2 (4%) | 0 | 2 (7%) |
| Chronic respiratory disease, COPD, or asthma | 9 (11%) | 6 (13%) | 1 (20%) | 2 (7%) |
| Active smoker | 2 (2%) | 1 (2%) | 0 | 1 (3%) |
| Immunocompromised§ | 3 (4%) | 0 | 0 | 3 (10%) |
| Time from first symptoms to ICU admission, days | 7 (5–10) | 7 (6–10) | 8 (5–10) | 6 (5–10) |
| Time from first symptoms to intubation, days | 8 (6–11) | 9 (6–11) | 10 (5–10) | 8 (5–10) |
| Time from intubation to ECMO, days | 4 (3–6) | 4 (2–5) | 7 (7–9) | 6 (4–8) |
| Retrieval on ECMO by mobile ECMO retrieval team from another hospital | 61 (73%) | 34 (71%) | 3 (60%) | 24 (80%) |
| Volume-assist control ventilation | 83 (100%) | 48 (100%) | 5 (100%) | 30 (100%) |
| Ventilation parameters | | | | |
| $FiO_2$ | 100 (100–100) | 100 (100–100) | 100 (100–100) | 100 (100–100) |
| Positive end-expiratory pressure, cm $H_2O$‡ | 14 (12–14) | 14 (12–15) | 12 (10–12) | 14 (12–14) |
| Tidal volume, mL/kg predicted bodyweight‡ | 6·0 (5·7–6·4) | 6·1 (5·8–6·5) | 5·7 (5·7–6·0) | 6·0 (5·7–6·4) |
| Respiratory rate, breaths per min‡ | 29 (28–30) | 29 (28–30) | 30 (25–32) | 28 (28–30) |
| Plateau pressure, cm $H_2O$‡ | 32 (29–33) | 32 (30–32) | 29 (26–32) | 32 (29–35) |
| Driving pressure, cm $H_2O$¶ | 18 (16–21) | 18 (16–20) | 16 (16–20) | 19 (16–22) |
| Static compliance, mL/cm $H_2O$‡ | 22·1 (18·1–26·5) | 21·8 (18·4–26·4) | 22·5 (21·2–26·9) | 22·1 (18·0–25·0) |
| Mechanical power, J/min‖ | 24·7 (22·0–27·3) | 25·3 (22·3–27·1) | 24·3 (22·1–24·5) | 24·6 (21·9–28·0) |
| Ventilatory ratio‡ | 2·7 (2·3–3·2) | 2·7 (2·2–3·1) | 2·5 (2·1–3·0) | 2·8 (2·5–3·6) |

(Table 1 continues on next page)

| | All patients (N=83) | Alive and discharged from the ICU (n=48)* | Alive and still in the ICU (n=5)† | Died (n=30) |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Last blood-gas values pre-ECMO | | | | |
| pH | 7·32 (7·24–7·38) | 7·32 (7·25–7·40) | 7·31 (7·30–7·34) | 7·28 (7·21–7·35) |
| $PaO_2/FiO_2$ | 60 (54–68) | 60 (53–68) | 65 (49–68) | 61 (55–70) |
| $PaCO_2$, mm Hg | 57 (50–68) | 56 (50–61) | 62 (43–62) | 61 (55–74) |
| Plasma bicarbonate, mmol/L | 27 (24–32) | 28 (25–31) | 32 (21–33) | 27 (23–31) |
| $SaO_2$‡ | 90% (83–92) | 90% (82–92) | 90% (83–92) | 89% (84–92) |
| Arterial lactate, mmol/L | 1·6 (1·3–2·0) | 1·6 (1·3–2·0) | 1·6 (1·0–3·0) | 1·8 (1·4–2·1) |
| Laboratory values | | | | |
| White blood cell count, $\times10^9$ cells per L‡ | 13·2 (10·1–17·2) | 11·4 (10·0–15·4) | 15·0 (14·0–15·0) | 15·4 (11·6–18·0) |
| Lymphocytes, $\times10^9$ cells per L‡ | 0·9 (0·5–1·3) | 0·9 (0·6–1·4) | 1·4 (0·9–1·6) | 0·7 (0·5–1·1) |
| Serum creatinine, μmol/L‡ | 82 (62–162) | 69 (59–103) | 112 (56–169) | 105 (70–221) |
| Serum bilirubin, μmol/L | 12 (8–22) | 11 (8–28) | 19 (15–28) | 15 (10–20) |
| Haematocrit | 29% (25–35) | 31% (26–36) | 28% (27–35) | 28% (25–34) |
| Troponin, ng/L | 35 (20–44) | 29 (18–44) | 36 (29–102) | 42 (31–71) |
| Rescue therapy pre-ECMO | | | | |
| Any | 82 (99%) | 48 (100%) | 4 (80%) | 30 (100%) |
| Neuromuscular blockade | 80 (96%) | 47 (98%) | 4 (80%) | 29 (97%) |
| Prone-positioning | 78 (94%) | 46 (96%) | 4 (80%) | 28 (93%) |
| Inhaled nitric oxide or prostacyclin | 28 (34%) | 15 (31%) | 1 (20%) | 12 (40%) |
| Steroids | 6 (7%) | 3 (6%) | 2 (40%) | 1 (3%) |
| Almitrine | 1 (1%) | 1 (2%) | 0 | 0 |
| Renal replacement therapy | 4 (5%) | 1 (2%) | 0 | 3 (10%) |
| Cardiac arrest | 3 (4%) | 0 | 1 (20%) | 2 (7%) |

Data are median (IQR) or n (%). ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. $PaO_2/FiO_2$=ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen. $PaCO_2$=partial pressure of arterial carbon dioxide. RESP=Respiratory Extracorporeal Membrane Oxygenation Survival Prediction. $SaO_2$=arterial oxygen saturation. SOFA=Sequential Organ-Function Assessment. COPD=chronic obstructive pulmonary disorder. *Of the 48 patients discharged from the ICU, on July 10, 2020, 14 were still hospitalised or in a rehabilitation centre and 34 returned home. †Of the five patients still in the ICU, on July 10, 2020, one remained on ECMO. ‡Patients missing data. Data missing for 1–8 patients, except for lymphocytes (n=21). §Defined as haematological malignancies, active solid tumour, or having received specific anti-tumour treatment within 1 year, solid-organ transplant or infected with HIV, long-term corticosteroids, or immunosuppressants. ¶Defined as plateau pressure minus positive end-expiratory pressure. ||Mechanical power (J/min)=0·098 × tidal volume × respiratory rate × (peak pressure – 1/2 × driving pressure). If not specified, peak pressure was considered equal to plateau pressure.

*Table 1:* **Patient pre-ECMO characteristics according to their endpoint state on July 10, 2020**

states: in the ICU and weaned off ECMO and alive and out of the ICU. Because patients could die at any time during follow-up, either in the ICU or after discharge, the died state is the only final absorbing state (the final state that a patient can enter that once entered cannot be left). In this four-state model (appendix p 9), each box represents a state and each arrow represents possible transitions from one state to another.

After assessing patient status, participants who did not reach the final absorbing state were right-censored at the end of the observation period (July 10, 2020). A Cox model stratified on each possible transition was fitted to estimate transition (from one state to another) and state occupation (for each of the four states) probabilities over time; the percentages of patients occupying each possible state were represented simultaneously over time with a stacked probability plot and reported with their 95% CI on days 28, 40, 50, 60, 70, 80, and 90 post-ECMO initiation. Another figure (appendix p 15) individually displays all possible transition probabilities from one state to another over time. Mean state occupation times (ie, the expected length of stay in each possible state of the multi-state model) was also reported at the same timepoints. Finally, median on-ECMO time and length of ICU stay were established.

All the analyses were computed at a two-sided α level of 5% with R software, version 4.0.0.

### Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Among the 492 consecutive patients (figure 1) admitted to the Paris–Sorbonne University Hospital Network ICUs (Pitié–Salpêtrière [n=289]; Saint-Antoine [n=110]; and Tenon [n=93]) for COVID-19 (March 8 to May 2, 2020), 83 (Pitié–Salpêtrière [n=79]; Tenon [n=4]) received ECMO support (median age 49 [IQR 41–56] years; 61 [73%] men;

SAPS II median score 45 [29–56]). Their pre-ECMO characteristics according to their endpoint state on July 10, 2020, are reported in table 1. Briefly, pre-ECMO rescue procedures consisted of prone-positioning (n=78, 94%), continuous neuromuscular blockers (n=80, 96%), and nitric oxide (n=28, 34%). Median PEEP was 14 (IQR 12–14) cm $H_2O$, driving pressure was 18 (16–21) cm $H_2O$, and mechanical power was 24·7 (22·0–27·3) J/min. At cannulation, the median $PaO_2/FiO_2$ was 60 (IQR 54–68) mm Hg and $PaCO_2$ was 57 (50–68) mm Hg. For comparison, detailed characteristics of patients with COVID-19 in our cohort and in the EOLIA trial[3] group are reported in the appendix (pp 5–7).

Femoral–jugular cannulas were inserted in 79 (95%) patients, mostly with a large (29 Fr) drainage cannula, a median 4 (IQR 3–6) days after endotracheal intubation. The MERT brought 61 (73%) patients from non-ECMO centres. ECMO support successfully lowered tidal volume, respiratory rate, and plateau pressure during the 24 h following its initiation: median 2·5 (IQR 1·8–4·2) mL/kg for tidal volume, 20 (20–24 breaths per min for respiratory rate), and 27 (27–30) cm $H_2O$ for plateau pressure (table 2, appendix pp 10–12). Consequently, the mechanical power delivered to the lungs dropped to 6·1 (IQR 4·1–11·0) J/min. Arterial blood gases also normalised rapidly on ECMO (appendix pp 13–14).

On ECMO, 67 (81%) patients were prone-positioned, 80 (96%) received continuous neuromuscular blockers, five (6%) nitric oxide, and 17 (20%) high-dose corticosteroids (table 3). Median activated partial thromboplastin time ratios rose progressively over days 1–3 on ECMO: 1·3 (IQR 1·2–1·6) on day 1, 1·5 (1·3–2·0) on day 2, and 1·8 (1·4–2·6) on day 3.

On July 10, 2020, median follow-up was 104 (range 70–120) days. Complete follow-up on 60 days was available for 83 patients post-ECMO implantation, 80-day

| | All patients (N=83) | Alive and discharged from the ICU (n=48)* | Alive and still in the ICU (n=5)† | Died (n=30) |
|---|---|---|---|---|
| Type of ECMO support | | | | |
| Femoral–jugular, venovenous | 79 (95%) | 47 (98%) | 4 (80%) | 28 (93%) |
| Femoral–femoral, venovenous | 2 (2%) | 0 | 0 | 2 (7%) |
| Femoral–femoral, venoarterial | 1 (1%) | 0 | 1 (20%) | 0 |
| Femoral–jugular–femoral, venoarterial-venous | 1 (1%) | 1 (2%) | 0 | 0 |
| 29 Fr drainage cannula | 57 (69%) | 33 (69%) | 3 (60%) | 21 (70%) |
| Return cannula | | | | |
| 17 Fr | 2 (2%) | 1 (2%) | 0 | 1 (3%) |
| 19 Fr | 21 (25%) | 15 (31%) | 0 | 6 (20%) |
| 21 Fr | 42 (51%) | 21 (44%) | 4 (80%) | 17 (57%) |
| 23 Fr | 18 (22%) | 11 (23%) | 1 (20%) | 6 (20%) |
| ECMO blood flow L/min | 5·1 (4·6–5·5) | 5·1 (4·6–5·5) | 5·0 (4·0–5·3) | 5·1 (4·6–5·5) |
| Sweep gas flow, L/min | 5 (4–6) | 5 (4–7) | 3·5 (3·0–5) | 5 (4–6) |
| Membrane $FmO_2$ | 100% (100–100) | 100% (100–100) | 100% (100–100) | 100% (97–100) |
| Total SOFA score day 1 | 11 (9–14) | 10 (9–12) | 11 (9–17) | 12 (11–16) |
| Renal component of the SOFA score of 3 or greater | 20 (24%) | 7 (15%) | 2 (40%) | 11 (37%) |
| Cardiovascular component of the SOFA score of 3 or greater | 43 (52%) | 20 (42%) | 3 (60%) | 20 (67%) |
| Haematological component of the SOFA score of 3 or greater | 4 (5%) | 1 (2%) | 1 (20%) | 2 (7%) |
| Ventilation parameters | | | | |
| $FiO_2$ | 55 (40–80) | 60 (30–80) | 40 (30–70) | 55 (43–70) |
| Positive end-expiratory pressure, cm $H_2O$ | 12 (12–14) | 12 (12–14) | 12 (12–12) | 12 (12–12) |
| Tidal volume, mL/kg predicted bodyweight | 2·5 (1·8–4·2) | 2·9 (1·9–4·2) | 2·5 (2·3–2·8) | 2·2 (1·4–4·2) |
| Respiratory rate, number per min | 20 (20–24) | 20 (20–25) | 20 (20–24) | 20 (20–24) |
| Plateau pressure, cm $H_2O$ | 27 (27–30) | 27 (24–30) | 27 (27–27) | 28 (27–30) |
| Driving pressure, cm $H_2O$ | 12 (12–14) | 12 (12–14) | 12 (12–12) | 14 (12–15) |
| Compliance, mL/cm $H_2O$ | 12·5 (9·0–20·0) | 13·3 (9·6–20·1) | 15·9 (13·2–16·7) | 10·9 (7·7–18·8) |
| Mechanical power, J/min | 6·1 (4·1–11·0) | 6·8 (4·5–12·4) | 7·1 (5·6–11·1) | 6·1 (4·0–9·9) |
| Ventilatory ratio | 0·7 (0·4–1·1) | 0·8 (0·5–1·1) | 0·6 (0·4–1·0) | 0·7 (0·4–1·1) |
| Ventilation mode | | | | |
| Airway pressure release ventilation/bilevel PAPV | 70 (84%) | 42 (88%) | 4 (80%) | 24 (80%) |
| Volume-assist control ventilation | 13 (16%) | 6 (13%) | 1 (20%) | 6 (20%) |

(Table 2 continues on next page)

| | All patients (N=83) | Alive and discharged from the ICU (n=48)* | Alive and still in the ICU (n=5)† | Died (n=30) |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Blood gases on ECMO day one | | | | |
| pH | 7·40 (7·36–7·47) | 7·40 (7·37–7·46) | 7·32 (7·29–7·48) | 7·41 (7·34–7·48) |
| $PaO_2$, mm Hg | 82 (70–100) | 84 (71–101) | 79 (72–80) | 82 (64–98) |
| $PaCO_2$, mm Hg | 45 (40–50) | 47 (40–50) | 48 (43–51) | 42 (38–47) |
| $SaO_2$ | 96% (93–98) | 96% (94–98) | 96% (94–97) | 96% (92–97) |
| Arterial lactate, mmol/L | 1·7 (1·4–2·1) | 1·7 (1·4–2·1) | 2·1 (1·9–2·1) | 1·7 (1·4–2·1) |
| Laboratory values | | | | |
| Platelets, $\times 10^9$ cells per L | 236 (176–299) | 242 (187–286) | 375 (175–398) | 214 (139–305) |
| Haemoglobin, g/dL | 9·0 (7·9–10·2) | 9·6 (8·1–10·6) | 7·9 (7·7–10·5) | 8·5 (7·9–9·1) |
| Fibrinogen, g/L‡ | 6·7 (5·6–8·1) | 7·1 (6·0–8·4) | 5·2 (3·1–7·0) | 6·4 (5·3–7·9) |
| D–Dimers, ng/mL§ | 6890 (2350–19460) | 8065 (2110–19730) | 7495 (4502–12710) | 5620 (2970–10790) |
| aPTT ratio | 1·3 (1·2–1·6) | 1·2 (1·1–1·5) | 1·6 (1·2–1·6) | 1·4 (1·3–1·8) |
| Adjuvant therapy on ECMO day 1 | | | | |
| Any | 70 (84%) | 41 (85%) | 2 (40%) | 27 (90%) |
| Neuromuscular blockade | 70 (84%) | 41 (85%) | 2 (40%) | 27 (90%) |
| Prone-positioning | 7 (8%) | 6 (13%) | 0 | 1 (3%) |
| Inhaled nitric oxide | 3 (4%) | 1 (2%) | 0 | 2 (7%) |
| Renal replacement therapy | 12 (14%) | 4 (8%) | 2 (40%) | 6 (20%) |
| Pneumothorax | 2 (2%) | 1 (2%) | 0 | 1 (3%) |
| Cardiac arrest | 2 (2%) | 0 | 0 | 2 (7%) |

Data are median (IQR) or n (%). aPTT=activated partial thromboplastin time. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. $FiO_2$=fraction of inspired oxygen. $PaO_2$=partial pressure of arterial oxygen. $PaCO_2$=partial pressure of arterial $CO_2$. PAPV=positive airway pressure ventilation. SOFA=Sequential Organ-Function Assessment. *On July 10, 2020, of the 48 patients discharged from the ICU, 14 were still hospitalised or in a rehabilitation centre and 34 returned home. †On July 10, 2020, of the five patients still in the ICU, one remained on ECMO. ‡78 patients. §63 patients.

***Table 2:* Characteristics of the patients on ECMO day 1 according to their endpoint state on July 10, 2020**

follow-up was available for 75 patients, and 90-day follow-up was available for 65 patients (appendix p 8). The estimated probabilities of being in a particular state were 6% (95% CI 3–14) for on ECMO, 18% (11–28) for in the ICU and weaned off ECMO, 45% (35–56) for alive and out of the ICU, and 31% (22–42) for deceased 60 days post-ECMO initiation (table 4). The occupation probabilities of each of the four endpoint states and the mean time spent in each state on days 28, 40, 50, 60, 70, 80, and 90 post-ECMO are given in figure 2 and table 4. All possible transition probabilities from one state to another over time are shown in the appendix (p 15). The median durations of ECMO support were 20 (IQR 10–40) days and ICU stay were 36 (23–60) days (appendix p 8).

Major bleeding occurred in 35 (42%) patients with mouth, nose, and thorax being the main sites. Packed red blood cells were transfused into 64 (77%) patients on ECMO. With higher-level anticoagulation, haemorrhagic stroke occurring in four (5%) patients. For all ECMO-treated patients, rates of clogged circuits were 4% (n=3), intravascular haemolysis was 13% (n=11), severe thrombocytopenia during the first 3 days on ECMO was 6% (n=5), and infection at cannula insertion site was 23% (n=19; table 3). 38 (46%) patients required renal replacement therapy, ventilator associated pneumonia was diagnosed in 72 (87%), and bacteraemia was diagnosed in 40 (48%) patients. Of note, the incidence of bacteraemia was similar in patients who did or did not receive steroids, other immunomodulatory therapies such as tocilizumab, or antiviral agents. Causes of death are reported in table 3. 30 patients died.

## Discussion

Herein, we describe a large case series of patients who received ECMO support for the most severe forms of COVID-19 ARDS. They were treated in the Paris–Sorbonne University Hospital Network ICUs, comprising five intensive care units, which are experienced in managing ARDS and ECMO. ECMO indications were based on the EOLIA trial selection criteria with an upper age limit of 70 years, and patients received highly standardised ECMO care and general ICU care. Granular information on patients' pre-ECMO characteristics, daily management, and outcomes were analysed. Contrary to preliminary results from other studies that indicated dismal outcomes with 84–100% mortality of patients who had COVID-19 and were treated with ECMO,[9,29] the estimated 31% probability of day-60 mortality for our patients on ECMO was similar to those treated with ECMO in the EOLIA trial (35% at day 60)[3] or the large prospective LIFEGARD registry (39% at day 180).[21]

| | All patients (N=83) |
|---|---|
| SOFA score on ECMO day 3* | 11 (8–14) |
| SOFA score on ECMO day 7† | 11 (8–13) |
| aPTT ratio ECMO day 2 | 1·5 (1·3–2·0) |
| aPTT ratio ECMO day 3 | 1·8 (1·4–2·6) |
| Adjuvant therapies on ECMO | |
| Received continuous neuromuscular blockers | 80 (96%) |
| Prone-position | 67 (81%) |
| Number of sessions on ECMO during the first 7 days | 1 (0–2) |
| Nitric oxide or prostacyclin | 5 (6%) |
| High-dose corticosteroids | 17 (20%) |
| Renal replacement therapy | 38 (46%) |
| Received COVID-19 specific treatment | 63 (76%) |
| Remdesivir | 8 (10%) |
| Lopinavir and ritonavir | 19 (23%) |
| Tocilizumab | 8 (10%) |
| Hydroxychloroquine | 16 (19%) |
| High-dose corticosteroids before ECMO day 8 | 12 (14%) |
| Included in a randomised controlled trial on SARS-CoV-2 therapy | 13 (16%) |
| ECMO-related complications | |
| ≥1 ECMO-circuit changes | 22 (27%) |
| Intravascular haemolysis | 11 (13%) |
| Clogged circuit requiring change | 3 (4%) |
| Repeat ECMO needed after decannulation | 1 (1%) |
| Severe thrombocytopenia (<50 × $10^9$ cells per L) during the first 3 days‡ | 5 (6%) |
| ECMO setting or insertion changes§ | 4 (5%) |
| Heparin-induced thrombocytopenia | 2 (2%) |
| Massive haemorrhage | 35 (42%) |
| Oronasal bleeding | 20 (24%) |
| Haemothorax | 7 (8%) |
| Cannula | 5 (6%) |
| Other site | 13 (16%) |
| (Continued from previous column) | |
| Blood-product transfusion | |
| Patients who received ≥1 red blood cell units | 64 (77%) |
| Number of red blood cell units per patient | 3 (1–11) |
| Patients who received ≥1 platelet units | 11 (13%) |
| Patients who received ≥1 fresh-frozen plasma units | 9 (11%) |
| Patients who received ≥1 fibrinogen concentrates | 12 (14%) |
| Stroke | 5 (6%) |
| Ischaemic | 1 (1%) |
| Haemorrhagic | 4 (5%) |
| Antibiotic-treated cannula infection | 19 (23%) |
| Pulmonary embolism | 16 (19%) |
| Cardiac arrest | 11 (13%) |
| Tracheostomy | 25 (30%) |
| Pneumothorax | 9 (11%) |
| Antibiotic-treated ventilator-associated pneumonia | 72 (87%) |
| Number of episodes | 2 (1–3) |
| ≥1 antibiotic-treated bacteraemia episodes | 40 (48%) |
| Cause of death¶ | |
| Septic shock | 10 (33%) |
| Multiorgan failure | 7 (23%) |
| Stroke | 4 (13%) |
| Haemorrhagic shock | 4 (13%) |
| Cardiovascular shock | 2 (7%) |
| ECMO-device failure | 1 (3%) |
| Other | 2 (7%) |

(Table 3 continues in next column)

Data are median (IQR) or n (%). ECMO=extracorporeal membrane oxygenation. SOFA=Sequential Organ Function Assessment. aPTT=activated partial thromboplastin time. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *80 patients. †72 patients. ‡81 patients. §Included ECMO-cannulation switches from venoarterial to venovenous (n=1); venoarterial to venous–arteriovenous (n=1); and venovenous to venous–arteriovenous (n=2). ¶30 patients.

*Table 3:* **ECMO management and complications as of July 10, 2020**

The pre-ECMO characteristics of our patients with COVID-19 indicated great ARDS severity before ECMO support was initiated. Their mean $PaO_2/FiO_2$ (62 [SD 18] mm Hg) was lower than for patients in the EOLIA[3] (73 [30] mm Hg) or LIFEGARD[21] (71 [34] mm Hg) trials, while pre-ECMO respiratory system compliance, driving pressure, mechanical power, and other respiratory and ventilatory parameters were similar in all three studies. Notably, our patients with COVID-19 had lower respiratory system compliance and higher driving pressure than previously reported for most patients with COVID-19 receiving mechanical ventilation,[1,2] indicating extensive SARS-CoV-2-induced alveolar damage.[30] According to guidelines from 2017 and 2019 for the optimisation of care for the most severe ARDS forms,[31,32] 94% of our patients benefited from prone-positioning before ECMO (compared with 56% in EOLIA[3] and only 26% in LIFEGARD[21]).

Beyond providing adequate oxygenation, high blood-flow ECMO achieves a homogeneous ultraprotective ventilation strategy, most frequently using bilevel-positive airway pressure or airway pressure-release ventilation modes, with tight control of the driving pressure.[33,34] Our patients' pre-ECMO median mechanical power reached 24·7 (IQR 22·0–27·3) J/min, although a higher mortality risk for patients with ARDS whose value exceeded 17·0 J/min has been suggested.[35] Following ECMO initiation, tidal volume, driving pressure, and respiratory rate were markedly reduced in our patients, resulting in a major decrease of the median mechanical power to 6·1 (IQR 4·1–11·0) J/min, as previously reported.[21] In addition, ECMO prone-positioning, used for 81% of our patients with COVID-19 (*vs* only 10% of patients treated with ECMO in the EOLIA trial),[3] might

| | State occupation probability (95% CI)* | Mean days in each state (95% CI)† |
|---|---|---|
| **Day 28** | | |
| On ECMO | 35% (26–46) | 18·5 (16·7–20·4) |
| In ICU and weaned off ECMO | 30% (21–41) | 5·5 (4·0–7·0) |
| Alive and out of ICU | 17% (10–27) | 0·8 (0·4–1·4) |
| Died | 18% (11–28) | 3·2 (1·8–4·8) |
| **Day 40** | | |
| On ECMO | 23% (15–33) | 22·0 (19·2–25·0) |
| In ICU and weaned off ECMO | 23% (15–33) | 8·9 (6·7–11·1) |
| Alive and out of ICU | 31% (22–42) | 3·6 (2·2–5·0) |
| Died | 23% (15–33) | 5·5 (3·2–8·1) |
| **Day 50** | | |
| On ECMO | 15% (9–24) | 23·7 (20·4–27·2) |
| In ICU and weaned off ECMO | 21% (13–31) | 11·2 (8·6–13·9) |
| Alive and out of ICU | 39% (29–50) | 7·1 (4·8–9·3) |
| Died | 27% (18–37) | 8·1 (4·9–11·5) |
| **Day 60** | | |
| On ECMO | 6% (3–14) | 24·6 (21·0–28·6) |
| In ICU and weaned off ECMO | 18% (11–28) | 14·4 (11·2–17·8) |
| Alive and out of ICU | 45% (35–56) | 11·4 (8·0–14·3) |
| Died | 31% (22–42) | 11·0 (7·0–15·4) |
| **Day 70** | | |
| On ECMO | 1% (0–8) | 25·1 (21·4–29·3) |
| In ICU and weaned off ECMO | 12% (7–21) | 14·4 (11·2–17·8) |
| Alive and out of ICU | 52% (42–63) | 16·2 (11·9–20·1) |
| Died | 35% (26–46) | 14·4 (9·5–19·5) |
| **Day 80** | | |
| On ECMO | 1% (0–8) | 25·2 (21·4–29·6) |
| In ICU and weaned off ECMO | 8% (3–16) | 15·4 (11·9–19·4) |
| Alive and out of ICU | 56% (46–67) | 21·5 (16·5–26·3) |
| Died | 35% (26–46) | 17·9 (12·1–24·0) |
| **Day 90** | | |
| On ECMO | 1% (0–8) | 25·4 (21·4–29·8) |
| In ICU and weaned off ECMO | 6% (2–15) | 16·2 (12·4–20·5) |
| Alive and out of ICU | 56% (46–67) | 27·6 (21·0–32·9) |
| Died | 36% (27–48) | 21·4 (14·7–28·5) |

Data are probability (%; 95% CI) or mean (95% CI). Probabilities do not add up to 100 due to rounding. Probabilities calculated at each timepoint for the whole population of 83 patients, with right-censoring of patients who did not reach the final absorbing state at later timepoints. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. *Probability of being in each endpoint state at the defined day after ECMO initiation. †Mean number of days spent in each endpoint state on the indicated day after ECMO initiation.

*Table 4:* Outcomes

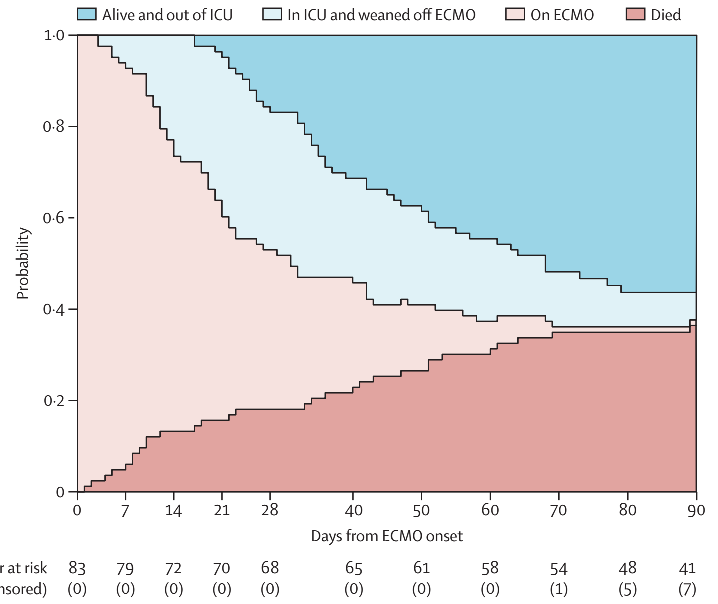


*Figure 2:* **Stacked probability plot for the multi-state model**
The plot illustrates the actual state occupation probabilities of being in each endpoint state—on ECMO, in ICU and weaned off ECMO, alive and out of ICU, or died—over the 90 days following ECMO implantation. The respective probabilities and mean lengths of stay (with 95% CI) in each of these four states are reported in table 4. See the appendix (p 15) for all possible transition probabilities from one state to another over time. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit.

have contributed to improving their outcomes. Indeed, a 2019 retrospective series of patients with severe ARDS showed that on-ECMO prone-positioning obtained higher ECMO weaning and survival rates.[22]

An autopsy-based histological analysis of the pulmonary vessels of patients with COVID-19 showed widespread thrombosis with microangiopathy, with alveolar capillary microthrombi being nine times more frequent in patients with COVID-19 than in those with influenza.[36] Consistent with other series,[19,20,37,38] we also observed an unusually high on-ECMO rate of proven pulmonary embolism (19%), an event not reported for the 156 patients treated with ECMO in the EOLIA trial.[3] Those thromboembolic events occurred, despite an early increase of our anticoagulation target for patients with COVID-19 receiving venovenous ECMO support, suggesting that other strategies, beyond systemic anticoagulation, are warranted to care for SARS-CoV-2 induced lung endothelial injuries. It should also be noted that haemorrhagic stroke occurred in 5% of our patients, which was more frequent than in the EOLIA trial (2%).[3] The higher anticoagulation regimen, and specific SARS CoV-2-associated vasculitis and critical illness associated microbleeds could explain this finding. However, the frequency of severe haemorrhagic events requiring transfusion in our study was similar to those of patients treated with ECMO in the EOLIA trial.[3]

Compared with the EOLIA trial of patients with severe ARDS (44% bacterial and 21% viral pneumonia) treated with ECMO,[3] in our study of patients with COVID-19, ECMO support (median 20 [IQR 10–40] days *vs* 11 [7–18] days) and ICU stay (36 [23–60] days *vs* 23 [13–34] days) lasted longer, highlighting the great severity of SARS-CoV-2 associated pulmonary damage and organ failure. Still, the needs for circuit changes were similar to those reported in a previous venovenous ECMO series.[3,21] Septic shock was the primary cause of death in 10 (33%) of 30 patients but none of them were converted to venoarterial or venoarterial-venous ECMO for cardiovascular support. Indeed, the use of these types of ECMO has been proposed in patients with septic shock with severe myocardial dysfunction and decreased cardiac index,[39] which was not the case in our patients. Lastly, our antibiotic-treated ventilator-associated pneumonia rate was higher (87%) than for patients in the EOLIA trial (39%),[3] and might reflect the longer mechanical ventilation or specific SARS-CoV-2 induced immunoparalysis. It should also be noted that few of our patients received high-dose corticosteroids.

We acknowledge several limitations to our study. First, our results have to be considered preliminary, as some patients remained in the hospital and day-90 post-ECMO outcomes were not available for all patients. However, we used a time-to-event analysis, which allowed estimation of the probabilities of remaining on ECMO, ECMO weaning, ICU discharge, or death over time, taking into account the fact that some patients' follow-up was censored.[28] Also, on July 10, 2020, we carefully updated follow-up of all included patients to ensure the absence of informative censoring for unbiased estimations. Second, our patients were treated in a high-volume ECMO university hospital network experienced in the care of the most severe forms of ARDS that might limit the generalisability of our observations. Third, indication for ECMO and other selection and information biases might have existed due to the limited size of our cohort of patients. Fourth, although the characteristics and outcomes of our ECMO-supported patients with COVID-19 were similar to those reported in a series of ECMO-treated patients with severe ARDS before the pandemic, we were not able to compare our patients' outcomes to those of patients with COVID-19 who were not ECMO-supported. Fifth, only data for thrombocytopenia occurring during the first 3 days of ECMO were collected, which might have underestimated the actual rate of this complication.[33] Lastly, we did not collect data for patients' viral load and cannot ascertain the potential benefits of prone-positioning on ECMO, which might represent areas for future studies.

In conclusion, the survival of ECMO-rescued very sick patients with COVID-19 was similar to that reported in studies on ECMO support for severe ARDS published in the past few years.[3,21] Should another COVID-19 wave occur, ECMO should be considered at an early stage for patients developing profound respiratory failure, despite optimised conventional care, including prone-positioning. Longer-term follow-up of these patients is also needed to evaluate the potential pulmonary, physical, and psychological sequelae of COVID-19.

#### Contributors

MS, GL, AM, GV, DL, EB, AB, JC, PM, SN, PB, PL, AD, BG, JMC, MF, MD, and AC were involved in data generation. MS, DH, and AC were involved in analysis of the data. MS, DH, and AC wrote the manuscript. All authors contributed to the revision, and read and approved the final version of the manuscript. AC takes responsibility for the integrity of the work as a whole, from inception to published article.

#### Declaration of interests

MS reports lecture fees from Getinge, Drager, and Xenios, outside of the submitted work. AD reports personal fees from Medtronic, Baxter, Hamilton, and Getinge; grants, personal fees, and non-financial support from Philips; personal fees and non-financial support from Fisher and Paykel; grants from French Ministry of Health; grants and personal fees from Respinor; grants and non-financial support from Lungpacer, outside of the submitted work. JMC reports personal fees and non-financial support from Drager, GE Healthcare, Sedana Medical, Baxter, Amomed, Fisher and Paykel Healthcare, Orion, Philips Medical, and Fresenius Medical Care, and non-financial support from LFB and Bird Corporation, outside of the submitted work. MD received fees from Lungpacer (expertise, lectures). AC reports grants from Getinge, personal fees from Getinge, Baxter, and Xenios, outside of the submitted work. GV reports grants and personal fees from BioMérieux, grants from SOS Oxygène, and grants from Janssen, outside of the submitted work. All other authors declare no competing interests.

#### Data sharing

Individual patient data reported in this Article will be shared after de-identification (text, tables, figures, and appendices), beginning 6 months and ending 2 years after Article publication, to researchers who provide a methodologically sound proposal and after approval of an internal scientific committee. Proposals should be addressed to alain.combes@aphp.fr. To gain access, data requestors will need to sign a data access agreement. The data from this study are not currently part of any other international collection of data.

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